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09/501,643	02/10/2000	Dr. Larry Sklar	UNME-0070-1	4170

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EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	18

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/501,643	SKLAR ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-27,46 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-27,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 11/15/02 in Paper No. 17 is acknowledged and has been entered. Claims 1, 9, 13, 14, 26, 46, and 47 have been amended. Currently, claims 1-7, 9-27, 46, and 47 are currently pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112/102/103

2. In light of Applicant's argument, the rejection of claims 9-10, 26, 46-, and 47 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

3. In light of Applicant's argument, the rejection of claims 1-3, 5, 7, 9-12, 15-19, and 26-27 under 35 U.S.C. 102(b) as being anticipated by Saros et al. (US 4,853,336), is hereby, withdrawn.

4. In light of Applicant's argument, the rejection of claims 4, 6, 13-14, 20-24, and 46-47 under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Kercso et a. (US 6,132,685), is hereby, withdrawn.

5. In light of Applicant's argument, the rejection of claims 25 under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Kercso et a. (US 6,132,685) and in further view of Farrell et al. (US 5,788,927), is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7, 9-27, 46, and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In this case, the specification does not provide any literal support for the recitation of "for hydrodynamically focusing said fluid flow stream and selectively analyzing particles". Applicant points to page 14, lines 7-16 for support, which the disclosure incorporates by reference US patents that disclose various types of flow cytometers that may be used with the instant invention. Applicant specifically amends the specification to insert two paragraphs from US Patent 5,395,588 which is one of the patents incorporated by reference, which briefly exemplifies a commercially available flow cytometer which relies on hydrodynamically focused fluid stream, i.e. FACSCan, to obtain support for the recitation of flow cytometer which relies on a hydrodynamically focused fluid system; however, the instant specification in itself still fails to provide literal support for such recitation. Additionally, none of the originally filed claims recited the

limitation in question. Recitation of claim limitation lacking literal support in the specification or originally filed claims constitutes new matter.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Scope of Enablement

7. Claims 1-7, 9-27, 46, and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of parameter controlled separation gas in a compatible flow cytometric device, does not reasonably provide enablement for use of any separation gas introduced into any flow cytometric device. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those skilled in the art to make and use

the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a flow cytometry apparatus for hydrodynamic focusing of fluid flow streams to selectively analyze particles in a plurality of samples separated by a separation gas which is specifically introduced from a means.

The state of the prior art- the prior art of record fails to disclose a flow cytometry apparatus for hydrodynamic focusing of flow streams for analysis of particles in a plurality of samples which are separated by a separation gas.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed standard flow cytometry device for hydrodynamic focusing will work with any uncontrolled amount of separation gas that is introduced into the fluid flow stream lines of the device to separate individual samples. Specifically, the instant specification teaches against introduction of any amount of gas in flow cytometric fluid flow stream tubings.

The amount of direction or guidance present- appropriate guidance is provided by the specification for a compatible flow cytometry apparatus to work in hydrodynamically fosusing fluid flow streams wherein the amount of separation gas is

specifically controlled by peristaltic flow rates through common tubing having specific parameter requirements. However, the specification fails to provide any guidance to enable the claimed standard flow cytometry apparatus to function with any amount of separation gas introduced into standard fluid flow stream tubing to separate individual samples.

The presence or absence of working examples- working examples are provided in the specification that show a compatible flow cytometry apparatus for hydrodynamic focusing wherein the amount of separation gas is specifically controlled by peristaltic flow rates through parametrically controlled tubing sizes and thickness. There are no working examples that show analogous results in any standard flow cytometry devices upon which any amount of separation gas is introduced in any sized fluid flow stream tubing, which are encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the apparatus as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a flow cytometry apparatus for hydrodynamic focusing of fluid flow streams to selectively analyze particles in a plurality of samples separated by a separation gas which is specifically introduced from a means. As recited, the instant flow cytometry apparatus for hydrodynamic focusing of fluid flow streams can function to selectively analyze particles in a plurality of samples separated by a separation gas regardless of the amount of gas or fluid flow rates introduced into the device.

The specification at page 9, first full paragraph, provides that in flow cytometric devices, air bubbles appear to be most effective at separating samples when there are no junctions or valves since junctions disturb or break up the bubbles and appear to allow the separated samples to come into contact with one another. The specification at page 14, last full paragraph, points out that both peristaltic pumps and air bubbles which are commonly used in flowing samples in clinical flow analyzers have not been applied to flow cytometry apparatus. More importantly, there is specific teaching in the flow cytometry art against air bubbles in fluid flow streams wherein optimally, the bubbles should be removed from samples prior to injection into fluid flow stream tubing. The specification further provides that Applicant has found and determined that peristaltic flow rates of +/-3 ul /second through common tubing (0.02 inch tubing, 10 rpm or higher) are parameters that are compatible with flow cytometry because of the requirement for hydrodynamic focusing in flow cytometric type detection.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable proper functioning of a flow cytometric device to have separation gas introduced into its fluid flow stream by a peristaltic pump, would be great as 2) there is no experimental evidence provided that would indicate that the claimed flow cytometry apparatus would properly function for particle analysis and detection, in the presence of any amount of separation gas or air bubbles in its fluid flow stream tubing; 3) there is no proper guidance that allows the claimed standard flow cytometry apparatus to function with any

amount of separation gas or air bubbles introduced into standard fluid flow stream tubing. Appropriate guidance is only provided for a compatible flow cytometry apparatus to work in hydrodynamically fosusing fluid flow streams wherein the amount of separation gas is specifically controlled by peristaltic flow rates through parametrically controlled tubing size and thickness, 4) the nature of the invention is a flow cytometry apparatus for hydrodynamic focusing of fluid flow streams to selectively analyze particles in a plurality of samples separated by a separation gas which is specifically introduced from a means, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that prior art teaches against use of any type of air bubbles or separation gas in flow cytometry devices due to hydrodynamic focusing requirement in performing flow cytometric type detection methods, and lastly 7) the claims broadly recite a flow cytometry apparatus for hydrodynamic focusing of fluid flow streams to selectively analyze particles in a plurality of samples separated by any amount of separation gas or air bubbles which are specifically introduced from a means, regardless of parameters used, i.e. amount of gas or fluid flow rates introduced or size or thickness of tubing, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3, 5, 7, 9-12, 15-19, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Saros et al. (US 4,853,336) in view of Weigl et al. (US 6,159,739).

Saros et al. disclose a single tubing (channel/conduit) continuous flow analyzer system in which a successive plurality of samples (liquid segments) containing biomaterial and test compounds (analysis mixtures) are separated by immiscible segments which permit delayed on-line mixing of the components in the mixtures in the single conduit (see Abstract, column 2, lines 40-55, column 4, lines 8-26 and Figure 4). Saros et al. specifically disclose a flow system comprising an autosampler for moving a plurality of samples, a means for introducing a separation gas (immiscible intervening

segment) between each sample, and the tubing for passage of fluid stream therethrough. The walls of the tubing have an expanded diameter sufficient to render the separation gas, non-occluding (see column 3). The autosampler includes a probe which aspirates the samples, test compounds, reagents (buffer fluid), and the separation gas. The autosampler is connected to a bidirectional linear drive means (see column 5, lines 1-10). Saros et al. disclose that the probe is coated with immiscible liquid. The movement or aspiration of the samples is effected by a peristaltic pump which is located downstream of the system tubing (see column 5, lines 14-21 and column 6, lines 52-55). Biomaterials in the samples are fluorescently tagged so that fluorescent signals associated with their function upon reaction with test compounds provide detectable events during analysis (see column 11, lines 23-36). In teaching that the probe and tubing in the flow system is coated with immiscible liquid, Saros et al. is, therefore, said to have inherently anticipated a hydrophobic probe or a probe coated with hydrophobic material.

Saros et al. differ from the instant invention in failing to disclose a flow cytometer for hydrodynamically focusing the fluid stream for analysis of particles in the samples as the fluid stream passes through the flow cytometer.

Weigl et al. disclose a device for 3-dimensional alignment of particles in microfabricated flow channels. Weigl et al. specifically disclose a flow module for reproducibly focusing particles into the measurement zone of a flow cytometer, wherein selective analysis of particles in a plurality of samples takes place (see column 3, lines 22-33). According to Weigl et al., optical flow cytometric measurement takes place by

arranging particles in a single file, typically by hydrodynamic focusing within a sheath fluid, then interrogating the particles by a light beam propagating orthogonal to the flow axis. Hydrodynamic focusing is a phenomenon that leads to a single file flow of particles as a result of the very small dimensions of the flow channel (see column 1, lines 17-52).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate a flow cytometer for hydrodynamically focusing a fluid flow stream so as to selectively analyze particles in samples as taught by Weigl into the flow analyzer as taught by Saros because Weigl specifically taught application of flow cytometric measurement zones that utilize hydrodynamic focusing in any microfabricated flow analyzers, such as for example, the flow analyzer as taught by Saros, having a means to move samples and a means to introduce a separation gas. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate flow cytometric measurement modules as used by Weigl into the flow analyzer as taught by Saros to create a versatile flow cytometric system capable of analyzing various sample particles because Weigl specifically taught widespread application of flow cytometric measurement modules in analyzing microscopic particles for determining physical and chemical properties in the fields of hematology, immunology, genetics, parasitology, oncology, etc.

9. Claims 4, 6, 13-14, 20-24, 46, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Weigl et al. (US

6,159,739) as applied to claims 1-3, 5, 7, 9-12, 15-19, and 26-27 above, and further in view of Kercso et a. (US 6,132,685).

Saros et al. and Weigl et al. have been discussed supra. Saros et al. and Weigl et al. differ from the claimed invention in failing to disclose the source well, as a well plate comprising 96, 384, or 1536 source wells. Saros et al. and Weigl et al. further differ in failing to disclose that the flow tubing or channels are made of polyvinyl chloride (PVC).

Kercso et al. disclose high throughput microfluidic flow systems for analyzing a large number of sample compounds. The samples to be analyzed are contained in standard multiwell microtiter plates such as those having 96, 384,1536, or higher numbers of wells and are transferred sequentially from the wells into a tubing or channel system. These multiwell plates travel along a conveyor system between an input stack and an output stack, and are sequentially aligned in the input port for autosampling by a tubular autosampler (pipettor) which extends below affixed to the microfluidic channel substrate (see column 3 and 11). These microfluidic flow channels are fabricated on the planar substrate comprising polymeric materials which are inherently hydrophobic such as polyvinylchloride (PVC) and polyurethane.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the sample source taught by Saros as modified by Weigl, with the microtiter plates taught by Kercso because Saros specifically taught sequentially analyzing a successive numbers of samples which are separated by immiscible segments in order to effect analysis of a plurality of samples using the flow

cytometer as taught by Weigl and Kercso specifically taught the advantage of using multiwell plate sampling for handling and sequentially introducing even larger numbers of samples to effect analysis thereto. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the multiwell plates of Kercso into the flow analyzer taught by Saros as modified by Weigl because Kercso specifically taught the added advantage of rapid and expedient analysis of large numbers of samples and test compounds in small volumes achieved by their sequential introduction from multiwell structures into automated flow analyzer and microfluidic systems.

Saros et al., Weigl et al., and Kercso et al. differ in failing to disclose that the flow tubing or channels made of PVC have an inner diameter of 0.01 to 0.03 inches and a wall thickness of 0.01 to 0.03 inches, such as recited in claim 13 or an inner diameter of 0.02 inches and a wall thickness of 0.02 inches, such as recited in claim 14. Further, Saros et al. and Kercso et al. fail to disclose that a portion of the fluid stream passing through the pump is contained within a tube having an internal diameter of 0.02 inches or less, such as recited in claim 46 and 47. Saros et al. and Kercso et al. also fail to disclose that the probe has a conical tip and the source wells on the microwell plates have conical shapes as well.

However, it is maintained that parameter requirements in flow systems or microfluidic channels such as inner diameter of 0.01 to 0.03 inches and wall thickness of 0.01 to 0.03 inches, or volumetric capacity of tube having an internal diameter of 0.02 inches or less ,or shape requirements of autosampling probe tips such as tubular or

conical shapes/structures are all result effective variables which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum parameter of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 13, 14, 4, 24, and 46-47 are for any particular purpose or solve any stated problem and the prior art teaches that flow analysis system requirements often vary according to the samples, types, and numbers thereof, being analyzed and various parameters taught by the prior art appear to work equally as well; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable parameters and requirements of the methods disclosed by the prior art by normal optimization procedures.

10. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saros et al. (US 4,853,336) in view of Weigl et al. (US 6,159,739) as applied to claims 1-3, 5, 7,

9-12, 15-19, and 26-27 above, further in view of Kercso et a. (US 6,132,685), and in further view of Farrell et al. (US 5,788,927).

Saros et al., Weigl et al., and Kercso et al. have been discussed supra. Saros et al., Weigl et al., and Kercso et al. differ in failing to teach that the well plate is mounted in an inverted position.

Farrell et al. teach a flow analyzer system which incorporates an automated sample aspiration design into its hydraulic system wherein a sealed sample source is inverted and moved relative to the probe of the autosampler for autosampling. The probe tip or needle of the autosampler penetrates the seal of the sample source to aspirate the sample contained within (see column 7).

The inverted mounting design of the well plate as recited in claim 25 has been specifically suggested by Farrell et al. for incorporation into flow analyzers such as those taught by Saros, Weigl, and Kercso and constitutes an obvious modification or design choice of autosampling or sample positioning, which is routinely varied in microfluidic or flow cytometric systems and which has not been described as being critical to the practice of the invention.

Response to Arguments

11. Applicant's arguments with respect to claims 1-7, 9-27, 46, and 47 have been considered but are moot in view of the new ground of rejection.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641 2/10/03 GRG

Christopher L. Chin

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